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Transurethral microwave thermotherapy: past, present and future

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The therapeutic use of heat has in the past engendered great enthusiasm and occasionally great disappointment. However, it now holds promise as an effective and durable, minimally invasive treatment for symptomatic benign prostatic hyperplasia (BPH). The increasing population age and the greater attention paid by older men to the symptoms of BPH means that the demand for treatment is almost limitless. Current studies of the natural history of prostatic enlargement suggest that it has relatively few serious connotations, and so great efforts have been made to lower the therapeutic burden for the patient. Transurethral resection of the prostate (TURP) in now being questioned as the "gold standard" treatment for every patient with symptomatic BPH because of the minor but significant rate of morbidity and failure in unselected patients. A host of interventional nonsurgical alternative treatments have emerged in the last 5 years [1–6]. The majority use thermal energy applied to the prostatic adenoma by the rectal, urethral or even an extracorporeal route. Energy sources include laser, focused ultrasound, radiofrequency and microwave energy. Treatments may be divided into those which demand some form of general or regional anaesthesia, often with a consequent need for an inpatient hospital stay, and those which can be easily accomplished without. For a treatment to truly not require anaesthesia, the energy must be precisely targeted, not require the use of rigid urethral instrumentation, and the treatment session must be of short duration. Transurethral microwave thermotherapy (TUMT) complies with all these conditions.

Microwave energy was first applied to the prostate for the purpose of treating cancer, because of the selective sensitivity of malignant cells to heat [7]. The basic principle was subsequently used to treat symptomatic BPH. It became apparent that higher temperatures were required to irreversibly damage BPH cells [6]. The treatments were soon applied via the urethral route and developed from multi-session to single-session therapies [8]. TUMT is a method of delivering the energy to the lateral lobes, while simultaneously cooling the treatment and urethral surfaces. The authors, with their experience of over 1500 treatments, review the current knowledge and discuss the future developments of TUMT.

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Intraprostatic heating

Heating is the primary effect of microwave radiation in biological tissues and comparison of different modalities shows that the athermal biological effects of microwaves are negligible [9].Thus the clinical benefit of TUMT must be related to the achieved intraprostatic temperature, which results from a complex interaction between the biological response to microwaves and the pattern of energy provided during the treatment in any individual.

Microwave therapy relies on the predictable field of heating within homogeneous biological tissue. The effectively heated volume is substantially reduced by the remarkably efficient homeostatic mechanisms for heat dissipation provided by the reactive increase in intraprostatic blood flow and the heat sink formed by the veins of Santorinis plexus. The combination of the predictable microwave field with the self-protective mechanism of the prostate means that properly designed microwave treatments for BPH are remarkably safe. However, the variable nature of each individual's prostatic structure and potential blood flow also means that the induced heat is, to a certain extent, unpredictable.

Results of treatment

The results of treatment will be discussed under the following headings: (1) Prostasoft 2.0 results, (2) durability of response, (3) morbidity, (4) dose response, (5) selection criteria and (6) higher-power treatments.

Table 1a. A review of TUMT data for individual symptom score changes compared to sham from baseline

Centre or country	n	Sham			TUMT		
		Pre	Post	Change (%)	Pre	Post	Change (%)
Lyon [29]	22	15.9	12.3	23	14.1	7.4	48
Nijmegen [20]	50	12.1	9.1	25	13.2	3.3	75
London [14]	40	14.2	12.8	10	14.5	4.3	70
US [30]	120	14.9	10.7	28	13.9	6.3	55
France [31]	251	12.8	11.4	11	14.0	6.7	52

Table 1b. A review of TUMT data for individual Q_{max} changes compared to sham from baseline

Centre or country	n	Sham			TUMT		
		ml/s	ml/s	Change (%)	ml/s	ml/s	Change (%)
Lyon [29]	22	10.0	8.2	–18	10.5	13.1	25
Nijmegen [20]	50	9.7	11.3	17	9.6	14.0	46
London [14]	40	8.6	9.2	7	8.5	13.0	53
US [30]	120	7.4	9.5	28	7.3	11.5	58
France [18]	251	10.7	9.7	–9	10.1	12.7	26

Prostasoft 2.0 results

Transurethral microwave thermotherapy is performed on an outpatient basis in all patients. Treatment details have been described elsewhere [8, 10]. One of the concepts of TUMT is to preserve the urethral surface from the worst effects of heat, by using conductive cooling from water circulating within the applicator. Each treatment with TUMT is a computer-controlled process with negative feedback control of the power applicator and the circulating coolant temperature. Thresholds are set in the computer control program, which defines the amount of energy supplied to the gland. The nature of the feedback control means that no one treatment is exactly the same as another.

Three versions of the operating software have been used in general clinical trials. The standard operating software for the Prostatron is version 2.0, and worldwide, remarkably similar clinical results have been reported from several centres [11–14]. Most studies use the Madsen-Iversen physician-guided symptom score (MSS) which ranges from 0 to 27. The mean entry level is usually 13 and the expected outcome is a fall to around 4. Similar symptom scores can be found in elderly non-complaining men [15]. Clinically significant changes are demonstrated in all studies. Mean peak flow rate (PFR) changes have ranged from 3 to 4 ml/s, representing a mean improvement of about 35% over baseline. The changes in symptom score and flow rate are noted from 6 weeks and persist over a period of 2 years [16]. There are now five sham-controlled randomized studies using this software, all of which have demonstrated that the effect of TUMT is greater than can be accounted for by either the associated urethral instrumentation or by any placebo effect (Table 1). In order to evaluate the clinical utility of TUMT, a randomized study comparing it with TURP was performed by Petterson, Dahlstrand and their colleagues from Sweden. TUMT was seen to have a lesser effect on uroflow but had a very considerable impact on symptoms with lower morbidity [16]. TUMT is shown to have nearly the same symptom reduction as the "gold standard" treatment. As expected, TUMT causes a significantly lesser change in PFR than seen with TURP.

Durability of response

The re-treatment rate after prostatectomy ranges up to 15% and depends on the interval of follow-up. It is unknown whether this re-treatment rate is related to the technique used, or to the dimensions of the cavity achieved by surgery. Clinical trials have shown a significant benefit from thermotherapy, although it is apparent that not all patients with BPH are completely relieved of their symptoms. In a long-term study at Charing Cross Hospital in London, 100 patients were followed, and at 1 year 11% had required TURP for persistent symptoms or high residual urine [17]. De la Rosette et al. presented the results of a group of 130 patients with the follow-up of 1 year [12]. In this group, 11 patients were additionally treated with TURP. In a study by Dahlstrand et al. of 39 patients treated with TUMT, 4 patients were considered non-responders and, therefore, underwent TURP [18]. Blute et al. presented the results of 150 patients with a follow-up of 1 year, and 19 patients were regarded as non-responders [11]. In contrast to these results, Van Cauwelaert et al. [19] and Tubaro et al. [13] show subjective and objective improvement, while the re-treatment rate is acceptably low. However, the durability of response needs a longer follow-up.

Morbidity

The TUMT treatment is well tolerated by the patients. Perception of discomfort varies from a mild feeling of

Table 2. The change in clinical parameters at 3 months relative to the final temperature achieved within the prostate with TUMT (*PFR* peak flow rate; *MSS* Madsen-Iversen symptom score)

Temperature achieved (average)		*n*	PFR % increase (absolute change)	MSS % increase (absolute change)
Low	(43.8°C)	13	34 (7.4–9.9)	73 (14.7–4.0)
Medium	(47.5°C)	16	43 (7.4–10.6)	76 (15.0–3.6)
High	(53.2°C)	10	79 (7.5–13.4)	90 (13.5–1.3)

Table 3. The proportion of subjects with 75% improvement (=success) in MSS and PFR in various TUMT studies

Study	MSS	PFR	MSS and PFR
General 2.0	48%	24%	17%
General 2.5	42%	40%	22%
Compressive	44%	11%	7%
Constrictive	59%	55%	41%
Low temperature	54%	8%	8%
High temperature	90%	50%	40%

perineal warmth and a mild urge to urinate to occasional significant discomfort. Distraction and reassurance are usually enough, but momentary interruption of microwave emission may be useful in those with major discomfort. Most patients experience perineal discomfort and urinary urgency for several days after treatment, but not usually longer. Occasionally haematuria is noticed. No tissue sloughing occurs, and urinary retention is expected in up to 25% of patients [6, 8, 10–14, 16, 20]. In these cases, a catheter may be necessary for an average of 7 days. This procedure is not complicated by urinary tract infections. Prograde ejaculation is maintained and sexual function is unchanged. In the vast majority of patients the semen quality is also unchanged [21]. No bladder neck contraction has been reported and no urethral strictures have been noticed thus far. From these data, we may conclude that urinary retention constitutes the sole major complication and may easily be managed with an indwelling catheter for approximately 1 week.

Dose response

On a conceptual basis, the increase in thermal dose can be seen with the evolution of thermal treatment modalities for BPH patients. Transrectal hyperthermia has been shown to have virtually no histological effect; nor does it cause much increase in PFR [22]. Transurethral hyperthermia without cooling of the applicator has a greater effect on the tissue, and some histological changes have been seen, but the effect on flow rate remains small [23]. TUMT has a much greater histological effect and causes significant changes in PFR.

The elevation of intraprostatic temperatures as measured by invasive thermometry during TUMT using version 2.0 operating software has been shown to be broadly correlated with clinical outcome [24]. Patients whose baseline temperature was increased by an average of 8°C over the course of the 1-h treatment had significantly better improvement in PFR and an improved clinical response as shown by MSS (Table 2). Of particular note is that the number of patients who had a successful outcome, as defined by either an increase in PFR or decrease of MSS of greater than 75%, was significantly greater among those in whom a higher temperature was achieved (Table 3).

Selection criteria

Analysis of treatment outcome demonstrates considerable variability in individual response. Some patients do surprisingly well, while other patients show almost no response to treatment. In an attempt to provide selection criteria, Devonec (personal communication) analysed the patient profile before treatment of a group of responders (n = 119) and non-responders (n = 111) to TUMT treatment. There was no difference in the two patient groups before treatment with regard to age, MSS, PFR, postvoid residual volume, or prostate volume. Devonec concluded that there are no clinical parameters either for prediction of clinical outcome or for selection of the ideal candidate.

Elasticity of the prostatic urethra has been previously discussed by Schäfer [25] in the description of specific types of obstruction. Plotting pressure and flow values from a pressure flow (P-Q) tracing of patients on an X-Y diagram gives a hysteresis curve with an unique pattern. At one extreme, represented by a stenosis of the urethra, the hysteresis plot is characterised by a low value of the minimum opening pressure and a steep increase in detrusor pressure during the passage from minimum to maximum flow, due to reduced elasticity of the flow controlling zone (constrictive obstruction). At the other extreme (pure compressive obstruction), the hysteresis plot is characterised by a high value of the minimal opening pressure, because there is a difficulty in opening the flow controlling zone, and only a small increase in detrusor pressure during the transition from minimum to maximum flow, because the urethra can be easily expanded to reach its maximum cross-sectional area. The two extremes of these specific types of obstruction are seldom encountered in routine clinical practice, but any patient can be classified as having one or other form predominating.

If TUMT is able to modify elasticity of the prostatic urethra, patients suffering from reduced elasticity should be ideal candidates for this treatment modality [26, 27]. Such a hypothesis has been tested in a retrospective analysis of a large European multicentre study [28]. The analysis showed that no single subjective or objective parameter of BPH severity had a significant correlation with clinical outcome after TUMT, although there was a trend for patients with lesser degrees of obstruction to do better. Constrictive obstruction was defined by a minimal urethral opening pressure (pmuo) value <45 cm H_2O and slope value > 2.5; compressive obstruction was defined by a pmuo value > 45 cm H_2O and/or a slope value < 2.5. The two groups were comparable at screening but differed significantly after treatment. Six months after treatment, the symptoms of BPH severity were significantly modified in both groups, with a trend towards a larger decrease in severity in constrictive patients than in compressive ones. No significant difference was found between the two groups with regard to symptoms or uroflow parameters. However, the change in objective parameters after treatment differed significantly in the two groups. Patients with a predominantly constrictive pattern of obstruction had significantly greater improvement in both maximum and average flow rates, as well as decrease in residual urine, than those with compressive obstruction. From a urodynamic standpoint, the change in the slope of the passive urethral resistance relation of constrictive patients brought them back to a near-normal P-Q relation.

Clinical response to microwave thermotherapy is highly variable, and no consensus has been reached on how success and failure should be defined. Different guidelines have been proposed, and some of them have been recently endorsed by regulatory authorities. Evaluation of clinical outcome by percentage improvement of MSS *and* maximum flow rate results in a success rate (> 75% improvement) of 41.4% and 7.0% in constrictive and compressive obstruction patients, respectively. The failure rate (improvement < 25%) was 17.2% and 70.4%, respectively.

In conclusion, it appears that the only possible way of identifying the patients who will respond best to TUMT using Prostasoft 2.0 is by formal measurement of the pressure-flow relationship. Adoption of such parameters in prospective trials should improve the overall results, durability of response and clinical utility of this treatment modality. Moreover, BPH is a complex disease, and urologists should maintain a central role in diagnosing the disease and in treating it when required. The urologist must be the expert on the disease, not just on its (surgical) treatment.

Higher-power treatments

Further modifications to the operating software have been made in recent years in order to provide greater clinical efficacy. Higher temperatures may be the only way to achieve the removal of the obstruction. Currently, the version of the operating software known as 2.5 is under evaluation. The programme is modified to provide more power at a maximum of 70 W and a higher rectal threshold leading to fewer treatment interruptions and an increase in the energy delivered to the prostate. Overall, the maximum that can be delivered rises from 194.4 kJ (average 110 kJ) with version 2.0 to 219 kJ (average 155 kJ) with version 2.5. Not all patients will achieve this level because of limitations imposed by the rectal and urethral alarms.

Simple clinical analysis of the outcome by means of PFR and MSS demonstrates a substantial advantage of 2.5 over the earlier version (Table 4). We believe that the great change in flow rate we have seen in patients receiving the 2.5 software treatment cannot be explained by anything other than a decrease of urodynamic obstruction, assuming the same contractility. However, there is a price to be paid in terms of morbidity. We feel that a catheter is needed in all patients for at least 1 week, and retention may be prolonged considerably beyond this. Cavities are frequently seen with ultrasound at 6 months (Fig. 1). As yet, selection criteria for the higher-power treatment have not been investigated. It is possible that it should only be used for patients who have severe obstruction as shown by pressure flow studies. We believe the relief of certain types and degrees of obstruction is worth the price of increased morbidity.

Table 4. Changes in clinical parameters after TUMT employing Prostasoft version 2.5 (data from Nijmegen; *RU* residual urine)

	Baseline	4 weeks	12 weeks	26 weeks
Number of patients	51	45	37	9
MSS	13.5	10.4	5.9	5.8
PFR (ml/s)	10.2	9.9	18.0	15.5
RU (ml)	103	38	24	29

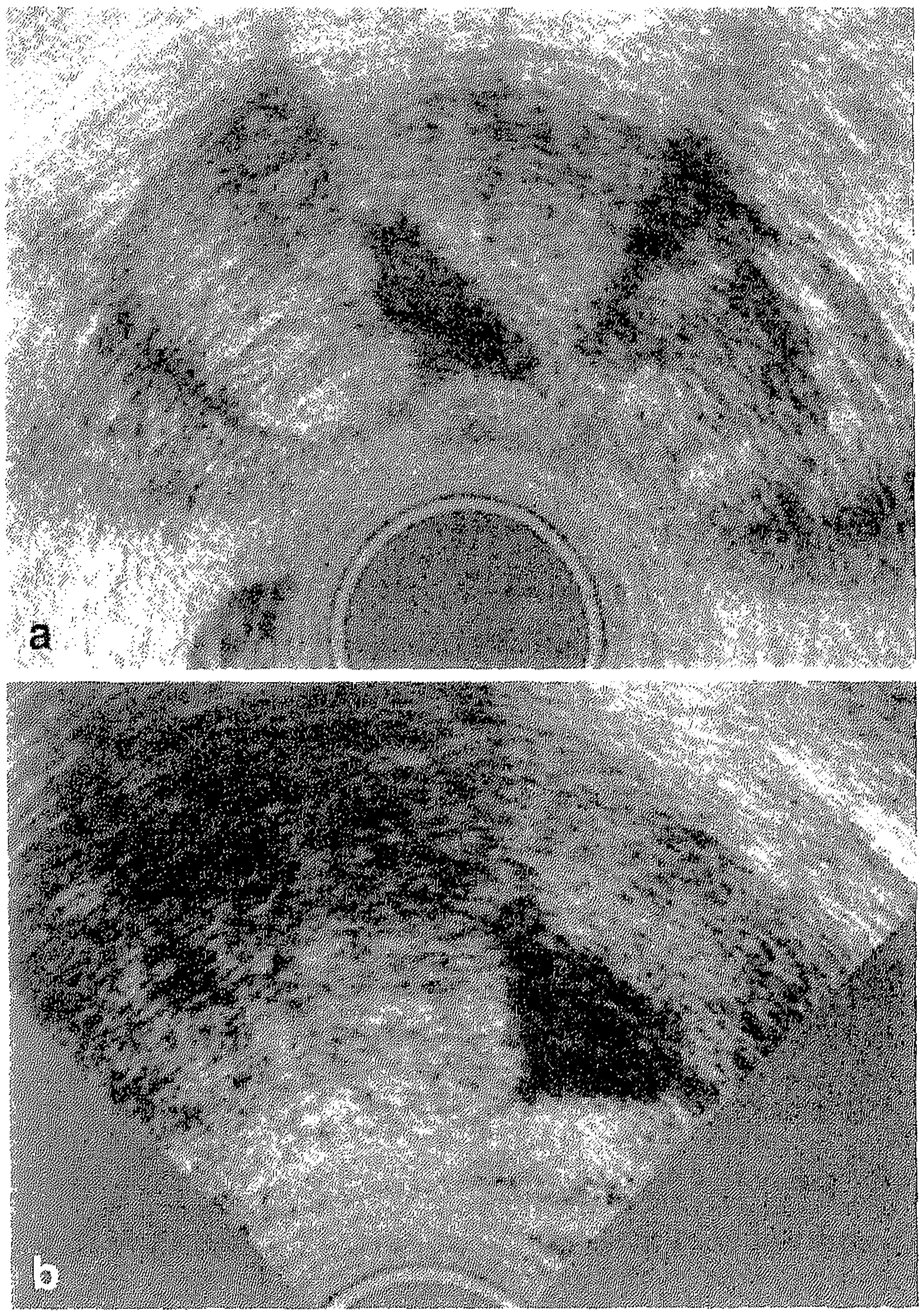

Fig. 1 a, b. Transrectal ultrasound of the prostate at 6 months post-TUMT using Prostasoft version 2.5 software. Unequivocally, a cavity can be seen in both the transverse (**a**) and the sagital (**b**) plane

Conclusion

The findings of improved clinical results in certain patient groups in some studies suggest that the full clinical benefit of TUMT has been under-reported. The objective must be to find the thermal dose, which will maintain a clinically significant reduction in symptoms with objective evidence of improved urinary flow and reduction in obstruction, while causing minimal post-treatment morbidity and still not necessitating anaesthesia. The maximum benefit of TUMT will be obtained only by selection of individual patients for specific therapeutic protocols.

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